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EXAMINER	
BORIN, MICHAEL L	
ART UNIT	PAPER NUMBER
1631	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/691,012	BUCHARDT ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-36,38-41,43-45 and 47-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36,38-41,43-45,47-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response filed 07/28/2010 is acknowledged. There is no change in claim language.

Status of Claims

Claims 34-36,38-41,43-45,47-73 are pending.

Claim Rejections - 35 USC § 112, first paragraph (enablement).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-36,38-41,43-45,47-73 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for extra-cellular administration of the oligomers from the broad genus of a "polyamide nucleic acid oligomer containing neutral amide backbone linkages", does not reasonably provide enablement for *in vivo* extracellular administration that produces an intracellular biological response (such as modulation of protein expression).

The rejection is maintained for the reasons of record and further in view of the responses to applicant arguments presented following the rejection.

The claims are directed to *in vivo* administration of a broad range of agents addressed as "polyamide nucleic acid oligomer containing neutral amide backbone linkages which is complimentary to a target nucleic acid". In all claimed embodiments said agent is required to interact with the target nucleic acid; since the target nucleic acid is located intracellularly, said agent has to be able to get inside a cell - and this is the main issue of enablement - to be able to "engender a biological response associated with target in a sequence specific manner", as recited in claim 34. All independent claims maintain the above requirement and differ in that they are directed to:

- treating living cells comprising extracellular administering to the cells (claim 34);
- treating a mammal comprising extracellularly administering to the mammal (claim 41);
- administering to living cells (claim 48);
- administering to a mammal (claim 58)
- administering to a organism to specifically bind to DNA or RNA (claim 61)

The only working example in the specification addressing the claimed effect on target nucleic acids in cells is example 70 (p. 103). Example 70 describes inhibition of expression of E2 mRNA of papilloma virus. The deficiencies of this example with regard to the claimed subject matter are the following:

1. Example 70 describes *in vitro*, not *in vivo* administration
2. Example 70 addresses peptide nucleic acid (PNA), which is a narrow embodiment, not a "polyamide nucleic acid oligomer containing neutral amide backbone linkages" as broadly claimed;
3. Example 70 is a prophetic experiment which lacks any teaching of an actual PNA

Paragraphs [0156]-[0163] (pages 36-38) address "therapeutic use" of the subgenus of PNAs, and inform that PNAs can be formulated in a conventional pharmaceutical composition, administered in a number of conventional ways, such as topical, intravenous, etc., and that such administration would encompass treatment of live cells.

While the only guidance from the above section of specification is that the PNAs can be administered *in vivo* as conventional pharmaceutical formulations, there is no guidance in the specification regarding *in vivo* delivery of PNAs into cells, and furthermore, regarding delivering agents other than PNAs; i.e. those selected from a broad genus of "polyamide nucleic acid oligomers" .

With regard to *in* vivo delivery of peptide nucleic acids (PNAs) into cells, there is no guidance in the prior art on how to administer *in vivo* "polyamide nucleic acid oligomers" so as to exert the claimed specific intracellular effect of "engendering a biological response associated with target in a sequence specific manner". Applicant's own publications, published long after the effective filing date of the instant application, emphasize the unpredictability of the art. The following is a review of said applicant's "after-filing" publications:

A. In 1994 Nielsen et al. (3 of 4 inventors of the instant application) published "Peptide Nucleic Acids (PNA), A DNA Mimic with a Peptide Backbone." At pages 5-6 it teaches:

ANTIGENE ACTIVITY
The ability of PNA to cause transcription elongation arrest imply a very interesting potential for PNA as gene targeted drugs at the dsDNA level, especially since oligonucleotide triplex formation is not able to arrest RNA polymerase unless the oligonucleotide is modified in a way that allows a covalent crosslink to the target to be formed (34-36). However, **another aspect apart from the cellular uptake issue has to be considered before this may be reality.** As mentioned earlier, strand displacement binding of PNAs Tlo, T4CT5, or T4CT2CT2 to dsDNA is inhibited at

Na+ concentrations above 50 mM (26, ***31)*** and thus presumably also at physiological conditions in the cell nucleus (although this has not been investigated). **Therefore, PNAs with the propensity of binding to dsDNA under in vivo conditions should be investigated.**
. . .

PROSPECTS
It should be clear from the above presentation t h a t **the development of PNA and the investigation of its physicochemical and biological properties is only in its infancy and that much work is still required to assess if it will be able to bear fruit in terms of new gene targeted drugs** and reagents and give new insight into the physical and biological properties of DNA and maybe even evolution.

B. Hyrup et al. (1996) (Inventor Nielsen co-author) teaches:

5. PNA as a Potential Antisense and Antigene Drug

The potential use of PNA as an antisense or antigene drug for sequence-specific modulation of gene expression has bright prospects. However, several issues must be addressed before reaching this ultimate goal. In vitro assays examining the effect of PNA on replication, transcription and translation all look very promising.[34,35,50,51] Low concentrations of PNA are sufficient to obtain the desired effects, the sequence specificity is high and, furthermore, the biological stability of PNA appears to be sufficient for the application of PNA as a drug.[14] The drawbacks include poor cellular uptake of PNA[52,53] and possibly the sensitivity of strand displacement complex formation to high salt concentrations. The cellular uptake may improve by attachment of lipophilic or other helper groups to PNA, by formation of PNA–DNA chimeras, or by the use of liposomes or other techniques for drug delivery. Moreover, the pharmacological properties of PNA have not been thoroughly investigated.

Page 20, right hand column-page 21, left hand column

The future prospects of PNA as a drug have still to be assessed. The poor cell permeability of PNA may indicate poor bioavailability, and issues like the pharmacological properties of PNA have to be addressed. It has been discussed that the high thermal stability of PNA–nucleic acid complexes could lead to decreased sequence specificity at physiological temperature.[66] While this concern is certainly legitimate, the use of shorter PNAs and/or backbone modified PNAs should allow the stability to be controlled.

The inventor's own teachings suggest that the utility of PNAs as pharmacological agents remained uncertain.

C. Basu et al. (1997) (page 482, first ¶, left hand column):

PNA activity as an antisense agent has been demonstrated *in vitro* and by microinjecting individual cells in culture (*9*). Microinjection of PNAs into cells was necessary because of poor cellular uptake (*10*) which was found to be 10 times less efficient than uptake of

> phosphorothioates in a variety of mammalian cells (*10*). One of the primary requirements for an oligonucleotide analog to be successful as an antigene/antisense agent is for it to be taken up by the cells in reasonable quantity so that it can reach its target in sufficient concentration. Since the PNAs suffer from poor cellular uptake, they have not been developed as an antigene/antisense therapeutic agent. To alleviate this situation, a strategy was developed to improve cellular uptake as well as to target the PNAs to specific cell types.

D. Finally, Ganesh et al. (review reference, one of the authors of which, P. Nielsen, is an applicant of this invention) teach that although peptide nucleic acids have been known since the beginning of the 1990's (i.e., time of filing the priority application of this application),

> ... some, but surely not all, of the promises expected from this molecule has materialized. Most success, has been achieved within diagnostic use of PNA oligomers in hybridization and PCR. The development of PNA oligomers into gene therapeutic drugs is still in its infancy. (p. 931)

Ganesh et al acknowledge that progress in the use PNAs as therapeutic drugs - **in particular concerning cellular delivery** - has been made only within the past couple of years (and refers to publications of years 1999-2000).

The same is discussed in the Background Section of US 6,472,209 (i.e., the patent against which the interference is being provoked):

> The success of an oligonucleotide analog as an antigene or antisense agent requires that the oligonucleotide be taken up by cells in reasonable quantities such that the oligonucleotide reaches its target at a sufficient concentration. PNA oligomers, however, have low phospholipid membrane permeability (Wittung et al., FEBS Letters 365:27-29 (1995)) and have been reported to be taken up by cells very poorly (Hanvey et al., Science 258:1481-1485 (1992); Nielsen et al., Bioconjugate Chem. 5:3-7 (1994); Bonham et al., Nucleic Acids Res. 23:1197-1203 (1995); Gray et al., Biochem. Pharmacol. 48:1465-1476 (1997)), which would appear to limit their potential uses in antigene and antisense approaches.

In addition, Summerton (US 5,142,047), while acknowledging that nucleic acid analogs with uncharged backbones "have a potential" for enhanced rate of passage across cell membranes, expresses concern that

There are, however, a variety of problems inherent in the structures of uncharged polynucleotide analogs of the type mentioned above. The structures are unstable in aqueous solution; do not allow assembly of different subunits in a defined order; and/or, the base-pairing moieties are not properly spaced for efficient binding to a target sequence.

Furthermore, Summerton teaches that configuring a polymer for inactivating target genetic sequences intracellularly may require conjugation to a carrier to favor its cellular uptake (col. 24, top).

Also, in addition, applicant previously argued that the publication of Hanvey et al. supports the enablement of the instant invention. It is reiterated here that microinjection administration, as addressed in Hanvey, does not read on *in vivo* treatment addressed in the instant claims. First, injection directly into nucleus of a cell can hardly be considered as "extracellular administration" addressed in the instant claims. Second, microinjection in general is not viewed as a method of *in vivo* administration.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art, one skilled in the art at the time the invention was made could not make and/or use the invention with the claimed breadth without an undue amount of experimentation. The skilled practitioner would first turn to the instant specification for guidance in practicing the full scope of the claimed method, however the specification only provides guidance to limited *in vitro* applications. As such, the practitioner would turn to the prior art for such guidance, however the prior art, at the time the invention was made, also lacked

knowledge on how to produce *in vivo* effects on intracellular nucleic acid targets by extracellular administration of PNAs, at least in a "naked", un-conjugated form. Finally, said practitioner would turn to trial and error experimentation to discover conditions of an *in vivo* administration without guidance from the specification or the prior art. Such represents undue experimentation.

Further, with respect to claims 38,43,53,61,70 drawn to "modification" of polypeptide expression, while the instant specification provides support for inhibition of protein expression, it does not provide support for any other modification (e.g., stimulation) of polypeptide expression.

Response to arguments

Applicant argues that "none of these publications indicates that the compounds do not produce at least some measurable level of the claimed biological response". To respond to this double-negative statement (emphasis added), it seems that the applicant rather than to point out at the evidence of the presence of the effect of PNAs prefers to point out at the absence of acknowledgement of the absence of effect. The point of the rejection is that with the lack of teaching in specification regarding *in vivo* delivery of PNAs into cells, much less of delivery of agents other than PNAs (i.e. those selected from a broad genus of "polyamide nucleic acid oligomers"), prior art also fails to provide guidance on how to achieve the effect t as claimed. In addition, as addressed in the rejection, applicant's own publications, published long after the effective filing date of the instant application, emphasize the unpredictability of the art.

With regard to discussing enablement demonstrated in US 6,472,209 ("Richelson patent over which applicant attempts to provoke interference), the reference is not considered because they are of post-filing date and enablement sufficiency of a specification is determined as of its filing date. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986). See MPEP 2164.05(a):

Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed.

With regard to the cited Federal Circuit's decision in *Agilent Technologies, Inc. v. Affymetrix, Inc.*, which addressed the issue of written description support for an interference count, in the instant case, first, the issue is enablement, not written description as in *Agilent*. Examiner wishes to point out that every application is examined on its own merits, and Examiner does not have information whether the enablement issues have been applicable to situation in *Agilent*.

Second there is no interference count being considered in the instant case as there no claims deemed allowable. Further, the interference has not been properly provoked in the instant case, even though the instant claims are copied from Richelson (US 6472209). As explained in the preceding Office action:

"At the time of filing applicants stated:

> In their claims 34-47, Applicants have copied claims 1, 2, 5, 10, 16-19, 24, 32-34, 43 and 52 of U.S. Patent No. 6,472,209, issued on October 29, 2002. Other added claims are at least directed to substantially the same subject matter as claims that issued in U.S. Patent No. 6,472,209. Since this amendment is being filed prior to October 29, 2003, Applicants have complied with the requirements of 35 USC § 135(b)(2) as well as 37 CFR 1.604(b).

Applicant's citation to 37 CFR 1.604(b) is in error. Since applicant was seeking to provoke an interference between a patent and an application, the application was subject to 37 CFR 1.607.

It is noted that the rules regarding interferences have changed since applicant's original filing and that 37 CFR 41.202 now applies:

> ***§ 41.202 Suggesting an interference.***
>
> (a) *Applicant.* An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must:
>
> (1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference,
>
> (2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts,
>
> (3) For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a),
>
> (4) Explain in detail why the applicant will prevail on priority,
>
> (5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification, and
>
> (6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter.

Applicant is invited to satisfy the requirements of the above rule 37 CFR 41.202 if he still wishes to provoke an interference."

Claim Rejections - 35 USC § 102.

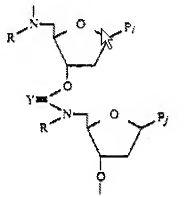
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 34-36,41,48-51,58,59,65-68 remain to be rejected under 35 U.S.C. 102(e) as anticipated by Summerton et al (US 5,142,047).

The instant claims are drawn to methods of treatment by *in vivo* administration of a polyamide nucleic acid oligomer containing neutral amide backbone linkages which is complementary to a target nucleic acid, under conditions wherein said oligomer engenders a biological response associated with said target. The claims specify that the administration is "extracellular". Claims 34-36,38-41,43-47 are directed to method of "treating living cells", whereas methods of claims 48-73 are directed to methods "comprising administering" said oligomer. Further, claims are directed to treating either cells, or mammals or organism (claims 34-36,38-40, claims 41-45,47, 58-64, and claims 65-73, respectively).

Summerton et al (US 5,142,047)[1] teach therapeutic administration of polymer composition effective to bind to a single-stranded polynucleotide containing a preselected target sequence of bases. See Abstract. The composition is composed of linked-subunit heteromeric polymer molecules, such as polymer comprised of subunits "B" and connected by amide backbone linkages. A part of the polymer structure, for two moieties "B", oligomer B-B, is exemplified in col. 5:



wherein, for Y=O, the formula demonstrates an "oligomer containing neutral amide backbone linkage", and is a part of "polyamide nucleic acid oligomer" which contains "neutral amide backbone linkages". Note that applicant maintains the argument that the compounds disclosed in Summerton et al. contain urethane, rather than amide linkage. Examiner maintains that the instant claims use open language "containing" (which is equivalent to "comprising"): "containing neutral amide backbone linkages". As such the structure -O–CO-NR- in Summerton et al is viewed as containing neutral amide backbone linkage (underlined) as instantly claimed.

[1] Exemplary reference of multiple patents of the same applicant

The reference addresses use of the polymer composition for inhibiting biological activity of a single-stranded polynucleotide (col. 7, lines 45-47), disease-specific mRNA in particular (paragraph bridging columns 16-17). As the polymers of Summerton are binding compounds having desired binding activity to selected target sequence (col. 5, lines 1-7, and col. 16, bottom), and a target sequence is a single-stranded polynucleotide (col. 4, bottom), the oligomers of 5,142,047 read on oligomers administered as per the instant invention.

With respect to claims 35,49,66 directed to detecting biological response, as argued by applicant, disclosure of use to bind *in vivo* binding to target polynucleotides inherently teach monitoring the organism and detecting a biological response (response of 01/09/2008, p. 8, last full paragraph).

With respect to claims 51,59,68 specifying that the administered oligomer has sequence specificity to nucleic acid that regulates the expression or encodes a polypeptide, the reference teaches that the oligomers are complementary to single-stranded polynucleotides (col. 7, lines 45-47), disease-specific mRNA in particular (paragraph bridging columns 16-17) or genes (col. 17, line 53).

Response to arguments

Applicant maintains the previously stated position that the carbamate structure can not be viewed as containing neutral amide backbone linkages. Examiner maintains that the instant claims use open language "containing" (which is equivalent to "comprising"): "containing neutral amide backbone linkages". As such the structure -O–

CO-NR- in Summerton et al is viewed as containing neutral amide backbone linkage as instantly claimed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin/
Primary Examiner, Art Unit 1631